significantly affect pulmonary clearance of M-pulmonis. The 5ppm exposure significantly retarded pulmonary clearance and M-pulmonis killing. Only macrophages from M-pulmonis exposed mice were able to kill M-pulmonis in-vitro. Maximal bactericidal activity occurred when the cellular plus noncellular lavage fluid fractions were used. Alveolar macrophages constituted about 95% of the total cells recovered by BAL from control and M-pulmonis exposed mice. Nitrogen-dioxide at 5 and 10ppm significantly reduced alveolar macrophage viability up to 3 days post exposure. Macrophage viability returned to the control value by 7 days post exposure. The authors conclude that nitrogen-dioxide decreases intrapulmonary killing of M-pulmonis by impairing alveolar macrophage function and viability.

5/AU,TI,SO,DE,AB/50 (Item 16 from file: 156)

AU- Zelikoff JT; Kraemer G-L; Vogel MC; Schlesinger RB

TI- Immunomodulating Effects of Ozone on Macrophage Functions Important for Tumor Surveillance and Host Defense

SO- Journal of Toxicology and Environmental Health, Vol. 34, No. 4, pages 449-467, 62 references, 1991

DE- DCN-204050; In vivo studies; Laboratory animals; Inhalation studies; Irritant gases; Oxidizers; Immune system; Free radicals; Alveolar cells; Cell migration

AB- The immunomodulatory effects of ozone (10028156) on macrophage function deemed important for tumor surveillance were studied in rabbits. Male New-Zealand-white-rabbits were exposed nose only to 1 part per million (ppm) ozone 2 hours daily for 3 days. They were killed immediately or 24 hours after the last exposure and the lungs were removed and lavaged. Lavage fluid total and differential cellularity was determined. The alveolar macrophages were recovered. The effects of ozone on random migration and chemotaxis toward zymosan activated serum were evaluated. The effects on resting and Escherichia-coli lipopolysaccharide (LPS) stimulated macrophage mediated cytotoxicity toward mouse-3T12 cells and production of tumor necrosis factor (TNF) toward L-M cells were assessed. Resting or zymosan stimulated production of hydrogen-peroxide and superoxide anion were measured. Ozone significantly increased the relative proportion of polymorphonuclear leukocytes in the lavage fluid immediately after exposure ended. The relative number of macrophages was not significantly affected; however, macrophage viability was significantly reduced. Ozone significantly decreased resting and LPS stimulated macrophage mediated cytotoxicity toward 3T12 cells at both time points. Product of TNF was not significantly affected. Ozone significantly decreased resting and zymosan stimulated production of superoxide, but had no effect on hydrogen-peroxide production. Ozone significantly decreased macrophage random migration immediately after exposure and significantly increased chemotaxis 24 hours after exposure ended. The authors conclude that repeated inhalation of 1ppm ozone causes inflammation and alters alveolar macrophage functions.

5/AU,TI,SO,DE,AB/51 (Item 17 from file: 156)

AU- Dahl AR; Sun JD; Birnbaum LS; Bond JA; Griffith WC Jr; Mauderly JL; Muggenburg BA; Sabourin PJ; Henderson RF

TI- Toxicokinetics of Inhaled 1,3-Butadiene in Monkeys: Comparison to Toxicokinetics in Rats and Mice

SO- Toxicology and Applied Pharmacology, Vol. 110, No. 1, pages 9-19, 38 references, 1991

DE- DCN-201948; Resins; Laboratory animals; Carcinogens; Inhalation studies; Butadienes; Metabolic study; In vivo study

AB- In order to compare uptake and metabolism of 1,3-butadiene (106990) in primates to that in rodents, three male cynomolgus-monkeys were exposed

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nose only to radiolabeled butadiene at nominal concentrations of 10, 300, or 8000 parts per million (ppm) for 2 hours. During exposure and for 96 hours post exposure, exhaled air and excreta were collected for analysis. The uptake of butadiene as a result of metabolism was much lower in monkeys than in rodents. For equivalent inhalation exposures, the concentrations of total butadiene metabolites in the blood were five to 50 times lower in the monkey than in the mouse and four to 14 times lower than in the rat. If the toxicokinetics of butadiene in people is more like that of the monkey than that of rodents, then the data suggested that people will receive lower doses of butadiene and its metabolites than rodents following equivalent inhalation exposures. This may be significant for assessing the risk to humans of butadiene exposure based on animal studies.

5/AU,TI,SO,DE,AB/52 (Item 18 from file: 156)
AU- Caldwell DJ; Alarie YC
TI- A Method to Determine the Potential Toxicity of Smoke from Burning Polymers: II. The Toxicity of Smoke from Douglas Fir
SO- Journal of Fire Sciences, Vol. 8, No. 4, pages 275-309, 25 references, 1990
DE- DCN-196051; Laboratory animals; In vivo studies; Combustion products; Plant substances; Wood; Toxic effects; Smoke inhalation; Analytical methods; Lethal concentrations
AB- A study was made of toxicity of Douglas-fir smoke in mice based on median lethal concentration (LC50), time to death and survivable exposure concentration (SEC). The UPitt-II apparatus for determining flaming combustion/toxicity of smoke was used. Energy and oxygen levels were varied to provide a range of conditions from just sustaining flaming above specimens to efficient flaming with high flame height. Douglas-fir specimens were 38 millimeters thick and had exposed surfaces for heat flux of 0.01, 0.016 or 0.028 square meter. Male albino-Swiss-Webster-mice were exposed head only to smoke. Toxic potency was determined from LC50 levels, and time to death was measured during 30 minute exposures and 10 minute post exposure periods. Oxygen and carbon-monoxide concentrations were measured in smoke, and carboxyhemoglobin (COHb) levels were measured in blood from exposed mice. Carbon-monoxide evolved slowly and was the primary toxicant during inefficient burning, while lethality in highly efficient burning conditions was not due to carbon-monoxide. Average LC50 for Douglas-fir smoke from all burning conditions was 113 milligrams per liter (mg/l). Lowest level producing death from 30 minute exposure was 76mg/l. COHb levels reached lethality in poor and moderate burning conditions, while low levels occurred with efficient burning. Time to death decreased as burning efficiency increased. Larger specimens showed more rapid drop in flame height, greater carbon-monoxide production and higher lethality. Cumulative hazard was greatest for most efficient burning where little carbon-monoxide was produced. Extrapolation to SEC for human exposure gave a value of 76mg/l for a 30 minute exposure, independent of burning conditions. The authors conclude that lethal effects of Douglas-fir smoke cannot be predicted from carbon-monoxide levels.

5/AU,TI,SO,DE,AB/53 (Item 19 from file: 156)
AU- Bond JA; Bechtold WE; Birnbaum LS; Dahl AR; Medinsky MA; Sun JD; Henderson RF

TI- Disposition of Inhaled Isoprene in B6C3F1 Mice
SO- Toxicology and Applied Pharmacology, Vol. 107, No. 3, pages 494-503, 23 references, 1991
DE- DCN-196025; Laboratory animals; Inhalation studies; Metabolic

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study; Pharmacodynamics; Butadienes; Hydrocarbons; Comparative toxicology

AB- The fractional absorption of inhaled isoprene (78795) was determined in B6C3F1-mice exposed to graded concentrations of isoprene vapor for up to 6 hours. The rates and modes of elimination of isoprene and its metabolites after the 6 hour exposure were also determined. Male mice were exposed to isoprene or to carbon-14 labeled isoprene at 20, 200, or 2000 parts per million (ppm) in a nose only exposure chamber. Steady state levels of isoprene were reached within 10 to 15 minutes at all levels of concentration. Depending on the concentration, from 52% to 73% of the metabolite associated radioactivity was excreted in the urine over a 64 hour post exposure period. Hemoglobin adduct formation reached near maximum between 200 and 2000ppm isoprene exposure concentrations, consistent with the theory that pathways for metabolism of isoprene were saturated. Retention of inhaled isoprene, which reflects in part the metabolism of isoprene, was linearly related to exposure concentrations up to 200ppm but decreased at 2000ppm. This differed from earlier studies in rats where the fractional retention of inhaled isoprene decreased with increasing exposure concentration over a range of exposures from 8 to 1500ppm. The percentage of inhaled isoprene that was metabolized was nearly two to three fold less in mice than in rats.

5/AU,TI,SO,DE,AB/54 (Item 20 from file: 156)

AU- Villaschi S; Giovanetti A; Lombardi CC; Nicolai G; Garbati M; Andreozzi U

TI- Damage and Repair of Mouse Bronchial Epithelium following Acute Inhalation of Trichloroethylene

SO- Experimental Lung Research, Vol. 17, No. 3, pages 601-614, 28 references, 1991

DE- DCN-195290; Laboratory animals; In vivo studies; Acute exposure; Chlorinated ethylenes; Inhalation studies; Toxic effects; Morphology; Pulmonary system; Histopathology; Cell damage; Cell growth; Dose response

AB- A morphological and morphometric study was made of the kinetics of epithelial damage and repair in the bronchial tree of mice exposed to one inhalation of trichloroethylene (79016) (TCE). Male BC3F1-mice were exposed nose only to TCE at 500, 1000, 2000, 3500 or 7000 parts per million for 30 minutes. They were sacrificed at 2 or 24 hours or 2, 5 or 7 days and lungs removed for morphometric assessment of bronchial epithelium. Some mice received intraperitoneal injection of 1 microCurie per gram tritiated thymidine 1 hour before sacrifice, and the labeling index was measured in bronchial epithelium cells. Blood absorption of TCE and clearance from blood were determined from axillary blood obtained immediately after exposure. TCE inhalation caused cytoplasmic vacuolation of nonciliated cells and did not affect ciliated cells. Although damage was seen throughout the bronchial epithelium, damaged cells were more numerous in small bronchi. Damage was maximal after 24 hours and was not dose related. Percentage of cells damaged was significantly greater in bronchi not more than 0.4 millimeter in diameter (67.0 +/8.5%) compared to bronchi of larger diameter (34.0 +/13.2%). Cellular repair was noted from 24 hours on and was significantly greater for lower TCE doses at 48 hours. Recovery was complete by 7 days. Cell damage was mainly composed of vacuolation of endoplasmic reticulum cisternae. Cytoplasmic granules disappeared between 2 and 48 hours at all TCE doses but reappeared after 5 days when numbers of vacuolated cells decreased. Labeling indices were maximal at 48 hours, and dividing cells with Clara cell features were observed. Blood absorption of TCE was dose related, and clearance was nearly complete within 3 hours. The authors conclude that a single TCE inhalation can selectively damage nonciliated cells (Clara cells) throughout the bronchial tree, the severity of which is dose related, and repair occurs through cell recovery and proliferation.

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5/AU,TI,SO,DE,AB/55 (Item 21 from file: 156)

AU- Siegel PD; George WJ

TI- Pharmacologic Manipulation of the Murine Pulmonary Biochemical Response to NO2

SO- Journal of Environmental Pathology, Toxicology and Oncology, Vol. 10, No. 4-5, pages 231-236, 21 references, 1990

DE- DCN-195081; NIOSH Author; Oxides; Nitrogen oxides; Laboratory animals; Lung cells; Respiratory system disorders; Inhalation studies; Inhalants; Toxic gases; In vivo study

AB- A pharmacological investigation was conducted to examine the contribution of influxing neutrophils to the biochemical profile of the oxidant damaged lung, as well as suggest the probable sources and nature of several proliferative and tolerant phase biochemical indices of the pulmonary response to irritant insult. CD-1-mice were exposed to nitrogen-dioxide (10102440) (NO2) or filtered room air using a nose only inhalation chamber. Lung tissue was removed 2 days following an acute or extended subacute exposure protocol. Hydroxyurea (127071) was injected intraperitoneally on a daily basis at a dose of 200mg/kg for a total of 10 days. The last injection was given on the last day of exposure to NO2. In test mice this treatment induced granulocytopenia. The biochemical profile of hydroxyurea induced granulocytopenic mice, two days following an acute exposure to NO2, differed from normal mice in that the NO2 induced enhancement of both beta-glucuronidase and lactate-dehydrogenase activities was significantly attenuated in the granulocytopenic mice. However, hydroxyurea treatment did not affect basal levels or increases in choline-kinase activity, protease inhibitors, protein, or lung weight following acute exposure to NO2. The NO2 induced damage observed histopathologically was also not changed in the granulocytopenic mice. The only alteration in the response to NO2 following subacute exposure on hydroxyurea treated mice was a greater increase in the protease inhibitor activity in the granulocytopenic mice. From these results, the authors suggest that the biochemical profile of the lung exposed to NO2 may actually reflect the stage of the lung's dynamic response to injury, which correlates with the observable histopathology. They also suggest that the relative contribution of a particular source to the biochemical profile of the injured lung may vary with the stage of the response to the irritant. If the biochemical changes in the lung are reflected in lavage fluid or serum, evaluation of enzymatic/nonenzymatic markers may be a useful tool in assessing alveolar damage.

5/AU,TI,SO,DE,AB/56 (Item 22 from file: 156)

AU- Jakab GJ; Hemenway DR

TI- Restraint of Animals Required for Nose-Only Inhalation Toxicologic Studies Suppresses Pulmonary Antibacterial Defenses

SO- Inhalation Toxicology, Vol. 1, No. 4, pages 289-300, 36 references, 1989

DE- DCN-189239; In vivo studies; Laboratory animals; Inhalation studies; Immune system; Physiological stress; Bacterial infections; Physiological response; Laboratory techniques; Immune reaction

AB- The effect of immobilization on pulmonary antibacterial defenses during nose only inhalation studies was examined in mice. Female Swiss-mice were restrained in immobilization holders for 4 hours daily for 1, 2, or 4 days before or 1, 2, or 4 days after nose only challenge with Staphylococcus-aureus or Proteus-mirabilis. Animals were killed 0, 4, 12, or 20 hours or 4 days after termination of the bacterial exposure and the lungs were removed. The effects on pulmonary bactericidal activity were evaluated by determining the percentage of viable bacteria remaining in the lungs. To assess the effects of conditioning, mice were placed in the restraining holders for 1, 2, or 4 days and

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challenged with S-aureus or P-mirabilis as before on days two, three, and five. Pulmonary bactericidal activity was determined as before. Restraining mice for 4 hours before S-aureus or P-mirabilis challenge significantly impaired pulmonary bactericidal activity. Bactericidal activity began increasing with increasing time after immobilization being completely restored after 20 hours. One day of conditioning significantly reduced the extent of bactericidal impairment. Two days of conditioning prevented any impairment. Restraining mice after bacterial challenge also significantly impaired pulmonary bactericidal activity. Conditioning for 2 days reduced the magnitude of the impairment. Conditioning for 4 days eliminated the restraint induced suppression. The authors conclude that immobilizing animals during inhalation toxicity studies impairs pulmonary antibacterial defenses. The effect of immobilization stress on other biological endpoints measured in pulmonary toxicological research is unclear. All animals used in inhalation toxicity studies should be properly trained to eliminate sources of error and possible misinterpretation of results.

5/AU,TI,SO,DE,AB/57 (Item 23 from file: 156)

AU- Nielsen GD; Kristiansen U; Hansen L; Alarie Y

TI- Irritation of the Upper Airways from Mixtures of Cumene and n-Propanol. Mechanisms and Their Consequences for Setting Industrial Exposure Limits

SO- Archives of Toxicology, Vol. 62, Nos. 2/3, pages 209-215, 28 references, 19881988

DE- DCN-176539; Aromatic hydrocarbons; Alcohols; Inhalation studies; In vivo studies; Laboratory animals; Pulmonary function; Mathematical models; Chemo receptors; Physiological response; Standards; Industrial hygiene

AB- Irritation of the upper airways by mixtures of cumene (98828) and n-propanol (71238) was studied in mice. Male Ssc:CF-1-mice were exposed nose only to mixtures containing 208 to 2872 parts per million (ppm) cumene or 1348 to 11786ppm propanol vapor for 30 minutes. Respiratory rates were monitored before, during and after exposure. A decrease in respiratory rate characterized by a pause before exhalation was taken as evidence of sensory irritation. The data were analyzed according to models that postulated that cumene and propanol acted independently or interacted competitively. Respiratory rates decreased during the first 2 minutes of exposure, the maximum decrease occurring at 2 minutes. A mixture containing 2872ppm cumene and 11786ppm propanol induced the largest decrease. The decreases in respiration rate gradually disappeared for mixtures containing less than 8500ppm propanol. A secondary decrease in respiration rate occurred after 30 minutes of exposure, the maximum decrease being induced by a mixture containing 1446ppm cumene and 10923 propanol. The data fit the competitive interaction model better than the independent action model. The authors suggest that cumene and propanol produce an interaction that is consistent with competitive agonism, indicating that they act on one common receptor unit in the upper respiratory system. The receptor may contain different binding sites which desensitize to different extents. The competitive interaction hypothesis is consistent with the additivity rule used for setting threshold limit values for occupational exposure to mixtures.

5/AU,TI,SO,DE,AB/58 (Item 24 from file: 156)

AU- Lee EW; Garner CD; Johnson JT

TI- A Proposed Role Played by Benzene Itself in the Induction of Acute Cytopenia: Inhibition of DNA Synthesis

SO- Research Communications in Chemical Pathology and Pharmacology, Vol. 60, No. 1, pages 27-46, 32 references, 19881988

DE- DCN-172433; Aromatic hydrocarbons; Organic solvents; In vivo

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studies; Laboratory animals; Nucleic acids; Biosynthesis; Bone marrow; Dose response; Inhalation studies; In vitro studies

AB- The effects of benzene (71432) on DNA, heme, and protein synthesis were studied in mice. Female ICR-mice were injected intraperitoneally (ip) with 220, 440, 880, or 1760mg/kg benzene or exposed nose only to 1000, 2000, or 3000 parts per million (ppm) benzene vapor for 4 hours. They were killed 30 minutes after ip and 4 hours after inhalation exposure and the extent of DNA, heme, and protein synthesis was determined. Bone marrow benzene concentrations were measured. Benzene given ip induced a dose dependent suppression of DNA synthesis. The 220, 440, 880, and 1760mg/kg doses induced bone marrow benzene concentrations of 41, 88, 161, and 284 micrograms per gram (microg/g), respectively. The 2000 and 3000ppm exposures reduced DNA synthesis by 15 and 33 percent, respectively. The 1000ppm exposure did not affect DNA synthesis. The bone marrow benzene concentrations corresponding to the 1000, 2000, and 3000ppm exposures were 37, 81, and 128microg/g, respectively. Benzene did not significantly inhibit heme or protein synthesis. In in-vitro experiments, mouse bone marrow cells and DNA-polymerase-alpha obtained from calf thymus DNA and DNA-polymerase-I obtained from Escherichia-coli were incubated with 0 to 7.8 millimolar benzene to assess the effects on DNA synthesis. Benzene inhibited DNA synthesis in mouse bone marrow cells and calf thymus DNA-polymerase-alpha, but not in E-coli DNA-polymerase-I. The authors conclude that benzene itself plays a significant role in inducing cytopenia in acute or subacute benzene toxicity. Its inhibitory effect on DNA synthesis results from inhibiting DNA-polymerase-alpha.

5/AU,TI,SO,DE,AB/59 (Item 25 from file: 156)

AU- Nielsen GD; Vinggaard AM

TI- Sensory Irritation and Pulmonary Irritation of C3-C7 n-Alkylamines: Mechanisms of Receptor Activation

SO- Pharmacology and Toxicology, Vol. 63, No. 4, pages 293-304, 38 references, 19881988

DE- DCN-172068; Peripheral nervous system; Neurological reactions; Toxic vapors; Chemical binding; Respiratory irritants; Toxic effects; Laboratory animals; Organic solvents

AB- The sensory and pulmonary irritation of normal three carbon (C3) to seven carbon (C7) alkylamines was studied with regard to the mechanisms of receptor activation of the nerves in the upper and lower respiratory tract. Adult male CF1-mice were exposed to n-propylamine (107108), n-butylamine (109739), n-pentylamine (110587), n-hexylamine (111262), or n-heptylamine (111682) by head only exposure and through tracheal cannulation. Sensory irritation was determined from the decrease in the respiratory rate of the noncannulated animals. Pulmonary irritation was observed in the cannulated animals at amine concentrations higher than those inducing sensory responses in normal animals. The concentration response curves for normal and cannulated mice were fitted to Michaelis/Menten equations. Values for the apparent dissociation constant for the amine induced decrease in respiratory rate in normal mice ranged from 285 parts per million (ppm) for propylamine to 13ppm for heptylamine after 10 minutes and from 319ppm to 18ppm for the C3 and C7 amines after 30 minutes. The apparent maximum response decreased with increasing chain length ranging from approximately 135 percent for propylamine to 77 percent for heptylamine, regardless of the exposure time. The amine levels producing a 50 percent decrease in the respiratory rate in normal animals were 184, 121, 97, 51, and 27ppm for propylamine, butylamine, pentylamine, hexylamine, and heptylamine, respectively. The amine levels producing a 50 percent decrease in the respiratory rate in cannulated animals were 416, 300, 128, 66, and 36ppm for the C3 to C7 compounds. Threshold limit values were estimated

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based on these results.

5/AU,TI,SO,DE,AB/60 (Item 26 from file: 156)
AU- Kristiansen U; Nielson GD
TI- Activation of the Sensory Irritant Receptor by C7-C11 n-Alkanes
SO- Archives of Toxicology, Vol. 61, No. 6, pages 419-425, 10 references, 19881988
DE- DCN-170378; Aliphatic hydrocarbons; Laboratory animals; In vivo studies; Organic vapors; Inhalation studies; Dose response; Pulmonary function; Sensory thresholds
AB- The sensory irritation effects of vapors of n-alkanes containing seven to 11 carbon atoms were studied in mice. Male Ssc:CF-1-mice some with tracheal cannulas were exposed head only to n-heptane (142825), n-octane (111659), n-nonane (111842), n-decane (124185), or n-undecane (821954) vapors at concentrations up to approximately 25000 parts per million (ppm) for up to 50 minutes. Respiration rates and body movements were monitored. Cessation of body movement was taken to indicate that the compounds were exerting anesthetic effects on the central nervous system. Decreases in respiratory rate were taken as evidence of a sensory irritation effect occurring. Body movements were observed during the entire exposure period for all concentrations of n-nonane, n-decane, and n-undecane. The concentration that reduced the respiration rate by 50 percent (RD50) during the first 10 minutes of exposure was 17400ppm for n-heptane. RD50s could not be determined for the other compounds. The decrement in respiration rate in cannulated mice exposed to n-heptane was similar to that of normal (uncannulated) mice. The decreases in respiration rate in cannulated mice exposed to the other alkanes were low compared to those of normal mice. Minimum threshold doses for inducing respiratory effects for n-heptane, n-octane, n-nonane, and n-decane were estimated using a thermodynamic activity model to be 1205, 605, 125, and 22ppm, respectively. A threshold dose for n-undecane could not be estimated. The authors note that the minimum threshold doses for n-heptane, n-octane, and n-nonane when compared with their their Danish threshold limit values (TLVs) 400, 300, and 200ppm, respectively, indicate that no sensory irritation would be expected for n-heptane and n-octane. For n-nonane exposure to the TLV concentration might produce irritation.

5/AU,TI,SO,DE,AB/61 (Item 27 from file: 156)
AU- Krzystyniak K; Fournier M; Trottier B; Nadeau D; Chevalier G
TI- Immunosuppression in Mice After Inhalation of Cadmium Aerosol
SO- Toxicology Letters, Vol. 38, Nos. 1/2, pages 1-12, 30 references, 19871987
DE- DCN-161494; Immunological tests; Heavy metals; Laboratory animals; Environmental pollution; Respiratory irritants; Air contamination; In vivo studies

AB- The in-vivo effects of cadmium (7440439) on the cellular and humoral immune responses of mouse spleen cell populations were assessed after a single pulmonary exposure to cadmium aerosol. Female C57B1/6-mice were subjected to either nose only exposure to aerosol cadmium at a dose of 0.88mg/m3 or to cadmium treated drinking water at levels of 5, 100, or 300 parts per million (ppm). Mice were immunized intravenously with sheep red blood cells (SRBC) at 1, 4, 7, or 14 days after aerosol exposure, and the Cunningham plaque forming cell assay was performed 4 days after immunization. A 60 minute inhalation exposure to cadmium aerosol significantly decreased the primary humoral response to sheep red blood cells between 5 and 18 days after aerosol exposure. The decline in the anti SRBC immunoglobulin-M (IgM) antibody titer of spleen cell supernatants was correlated with a decrease in the viability of spleen cells as determined by fluorescence microscopy

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between post treatment days five and eight. A general immunosuppression of the cellular responses of splenic lymphocytes occurred between five and 11 days after cadmium exposure. Chronic exposure to orally administered cadmium at doses between 100 and 300ppm reduced the anti SRBC IgM titer and the number of plaque forming cells without affecting the viability of spleen cell populations or the secretion of anti SRBC IgM antibody per cell. The authors conclude that the inhalation of cadmium aerosols induces a direct cytotoxicity affecting primary immune responses that differs from the chronic, oral cadmium induced suppression of the primary IgM response.

5/AU,TI,SO,DE,AB/62 (Item 28 from file: 156)

AU- Henry CJ; Kouri RE

TI- Specialized Test Article Administration: Nose-Only Exposure and Intratracheal Inoculation

SO- Occupational Safety and Health, Vol. 12, Inhalation Toxicology. Research Methods, Applications, and Evaluation, H. Salem, Editor; New York, Marcel Dekker, Inc., pages 121-134, 27 references, 19871987

DE- DCN-157566; Laboratory animals; Inhalants; Lung irritants; Laboratory testing; Pulmonary system disorders; Airborne particles; Airborne fibers; Breathing atmospheres; Biological effects

AB- Nose only inhalation exposure and intratracheal inoculation were described as methods which allow lung only exposures to hazardous materials. For nose only inhalation studies, animals were restrained in stocklike holders or whole body tubes and the nose of each animal protruded into either a chamber or channel where the aerosols were delivered. Over 70 percent of the material was deposited in the lung of the exposed animals, compared to 13 percent obtained by traditional exposure methods. There was little external body exposure and therefore little ingestion through preening. Particulate deposition and distribution were quite reproducible, with animal to animal variation of less than 20 percent. The major disadvantage to the nose only exposure system was that the animals were restrained and not allowed access to food or water during exposure. Results obtained using dotriacontane (544854) and catechol (120809) were described. For intratracheal inoculation, the material being studied was placed in the lung to allow direct interaction with lung cells. A blunt needle was carefully inserted down the throat of the animal, past the tracheal rings to the bifurcation of the lung where the material was injected. The technique was similar for rats, mice, and hamsters. The procedure was fairly simple and rapid, allowing injection of many animals per day. A wide range of treatment doses could be given and repeated over long periods of time; the chemicals bypassed the upper respiratory tract. The disadvantages to the method included the fact that this was not a normal route of exposure, anesthesia was required, the particle size delivered to the lung may not be uniform, and special care was needed to insure that animals survived the procedure.

5/AU,TI,SO,DE,AB/63 (Item 29 from file: 156)

AU- Kennedy GL Jr; Sherman H

TI- Acute and Subchronic Toxicity of Dimethylformamide and Dimethylacetamide following Various Routes of Administration

SO- Drug and Chemical Toxicology, Vol. 9, No. 2, pages 147-170, 15 references, 19861986

DE- DCN-152552; Organic solvents; Organo nitrogen compounds; Amides; In vivo studies; Laboratory animals; Acute toxicity; Chronic toxicity; Toxic effects; Biological effects; Hepatotoxicity

AB- The acute and subchronic toxicity of dimethylformamide (68122) and dimethylacetamide (127195) (DMAC) were studied in laboratory animals. Crl:CD-rats were administered DMF or DMAC orally or by inhalation in

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single doses or nine doses over a 2 week period. A 90 day feeding study was conducted. The animals were observed for signs of toxicity. Dead and surviving animals were necropsied. Eye irritation and dermal absorption studies were conducted in New-Zealand-white-rabbits. Male CD-1-mice were exposed by nose only to 0 to 2110 parts per million (ppm) DMF. Sensory irritation was evaluated by measuring the effects on the respiration rate. DMF caused moderate irritation in rabbit eyes. The corneal response cleared in 2 to 4 weeks. DMAC caused only a mild conjunctival irritation that cleared after 3 to 4 days. Single oral doses of 2250mg/kg or higher DMF and 7500mg/kg or higher DMAC were lethal to rats. DMF mortality was associated with liver damage. Median lethal doses calculated for DMAC were 5809 and 4930mg/kg in males and females, respectively. Median lethal concentrations for DMAC vapor were 2475ppm in female rats and 2475ppm for males. DMF at 1658ppm or higher produced sensory irritation in mice. Repeated oral and inhalation exposure to DMF and DMAC produced liver injury in rats. DMF, but not DMAC, caused lethality at doses of 2000 to 2500ppm. All rabbits receiving dermal exposures of 2000mg/kg DMF or DMAC showed anorexia and weakness, followed in many instances by cyanosis and death. These effects were more pronounced with DMAC. All rabbits showed acute hepatic necrosis. Feeding DMF or DMAC produced mild anemia and leukocytosis. Relative liver weights were increased in animals fed 1000ppm DMF. The authors conclude that the overall toxicologic profiles of DMF and DMAC are similar, and the liver is the target organ.

5/AU,TI,SO,DE,AB/64 (Item 30 from file: 156)

AU- Morgan A; Black A; Moores SR; Lambert BE

TI- Translocation Of 239Pu In Mice Following Inhalation Of Sized 239PuO

SO- Health Physics, Vol. 50, No. 4, pages 535-539, 13 references, 19861986

DE- DCN-146500; Respiration; Bioassays; Analytical methods; Equipment design; Radiation exposure; Lung function; Inhalants; Laboratory animals

AB- The translocation of plutonium-239 (15117483) after inhalation of plutonium-239-dioxide (22840342) (plutonium-dioxide) was studied in mice. Mice were exposed to plutonium-dioxide aerosols having median aerodynamic diameters of 0.8 to 2.2 microns in a nose/only inhalation apparatus. Concentrations were chosen to give initial alveolar depositions (IAD) of 10 to 1,000 becquerels. Selected mice were killed 2 days, or 3, 6, 9, 12, 18, or 24 months after dosing and the lungs, lung associated lymphatic tissue, liver, spleen, kidneys, femur, and gonads were removed and assayed for plutonium-239. A few eviscerated carcasses were also analyzed. After 12 months, the median relative organ concentrations of plutonium-239 as a percentage of the IAD were: lung, 2 percent; lung associated lymphatic tissue, 0.2 percent; femora, 0.02 percent; liver, 0.025 percent; spleen, 0.003 percent; kidneys, less than 0.0005 percent; and male or female gonads, less than 0.0002 percent. The amount of translocated plutonium-239 appeared to be independent of plutonium-dioxide particle size. The authors conclude that only small amounts of plutonium-239 are translocated to other organs from the lungs following inhalation of plutonium-dioxide particles.

5/AU,TI,SO,DE,AB/65 (Item 31 from file: 156)

AU- Brody AR

TI- The Early Pathogenesis of Asbestos-Induced Lung Disease

SO- Scanning Electron Microscopy, Vol. 1, pages 167-171, 21 references, 1984

DE- DCN-186966; Lemen; Lung cells; Cell function; Cell damage; Asbestos dust; Pulmonary system disorders; Laboratory animals; Pathogenicity; Inhalation studies; Mineral dusts

AB- New information obtained from animal models was presented to further

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complete current understanding of the initial cellular events which result in asbestosis. The studies reported were made in an attempt to elucidate in a rat model of asbestosis the initial events of asbestos (1332214) fiber deposition, translocation of fibers to the lung interstitium, the response of pulmonary macrophages and the mechanisms through which these cells were attracted to sites of initial asbestos deposition, and the developmental pathogenesis of the earliest anatomic lesion consequent to asbestos exposure. Studies of rats and mice inhaling dust for 1 hour in nose only exposure chambers indicated that a variety of particulates deposit at bifurcations of alveolar ducts. The majority of particles small enough to reach the alveolar level deposit on duct bifurcations. During the first hour of exposure, numerous fibers were taken up by type-I alveolar epithelial cells. These attenuated cells became highly phagocytic. A mechanisms existed whereby inhaled asbestos reaches the interstitial and blood spaces from which the fibers could be spread to other organs. Pulmonary macrophages played a significant part in the pathogenesis of several varieties of interstitial lung disease. Macrophages accumulated in significant numbers at bifurcations 48 hours after a 1 hour exposure to chrysotile (12001295) asbestos. Scanning electron microscopy indicated that over 90 percent of first alveolar duct bifurcations exhibited accumulations of significant numbers of macrophages. It appeared that asbestos fibers impacting on air space surfaces activated serum derived complement components of the alveolar lining layer to produce a chemotactic factor which could attract other cells and influence the development of emphysematous or fibrotic lung responses. A brief exposure to chrysotile asbestos caused a rapid influx of macrophages to the region of the first alveolar duct bifurcations, accompanied by local thickening of the epithelium and interstitium. These appeared to be the earliest measurable morphologic alterations related to inhalation of asbestos.

5/AU,TI,SO,DE,AB/66 (Item 32 from file: 156)

AU- Morgan A; Black A; Moores SR; Lambert BE

TI- Retention Of 239Pu In The Mouse Lung And Estimation Of Consequent Dose Following Inhalation Of Sized 239PuO2

SO- Radiation Research, Vol. 99, No. 2, pages 272-284, 18 references, 19841984

DE- DCN-131921; Lung burden; Radiology; Lung cells; Inhalants; Lung; Lung disorders; Animal studies; Lung fibrosis; Lung function; Pulmonary system; Lung irritants

AB- The distribution and retention of sized particles of labeled plutonium (7440075) (Pu) were investigated in the lungs of mice. Mice were exposed to labeled Pu via nose only inhalation exposure with particle sizes of 0.8 (small), 1.5 (medium), and 2.2 (large) microns. Initial alveolar depositions (IAD) selected ranged from about 1 to less than 1000 Becquerels (Bq). Mice were killed serially at various time intervals from 0 to 24 months post exposure, and lungs were removed and analyzed for Pu distribution. Urine and fecal samples were collected before killing. Pu retention was approximated in all cases, at least up to 18 months, by a two component exponential expression. When IAD were between 3 and 180Bq, about 90 percent of the Pu was retained with a half life time of about 40 days, and the remaining 5 percent with a half time of 150 days. At this dose range there was no effect of particle size or retention. At 840 to 1320Bq the half time was about 30 and 720 days for the two components, respectively. The retention was similar to that of the lower doses at 3 months, but a 6 month clearance was markedly slower. Larger particles cleared faster than medium particles. Mice survival was reduced to few animals at 18 months. Cause

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of death was pulmonary inefficiency. The apical lobe of the lung showed higher Pu retention than whole lung, while the diaphragmatic lobe showed less retention. Lung weight was not effected at 3, 6, and 12 months with low and medium IAD but high IAD affected lung weight at all times.

5/AU,TI,SO,DE,AB/67 (Item 33 from file: 156)

AU- Steinhagen WH; Barrow CS

TI- Sensory Irritation Structure-Activity Study Of Inhaled Aldehydes In B6C3F1 And Swiss-Webster Mice

SO- Toxicology and Applied Pharmacology, Vol. 72, No. 3, pages 495-503, 35 references, 19841984

DE- DCN-126958; Aldehydes; Animal studies; Inhalants; Exposure chambers; Respiratory irritants; Respiratory rate; Chemical structure; Chemoreceptors; Proteins; Threshold limit values; Sensory thresholds

AB- The sensory irritation potential of aldehydes was investigated in B6C3F1-mice and Swiss-Webster-mice. Aldehydes studied were acetaldehyde (75070), propionaldehyde (123386), butyraldehyde (123728), isobutyraldehyde (78842), valeraldehyde (110623), isovaleraldehyde (590863), caproaldehyde (66251), 2-ethylbutyraldehyde (97961), acrolein (107028), crotonaldehyde (4170303), 2-furaldehyde (98011), cyclohexanecarboxaldehyde (2043610), and benzaldehyde (100527). Groups of three or four mice were exposed to test atmospheres in a 2.7 liter head only exposure chamber for 10 minutes. Sensory irritation was quantified by measuring respiratory rate depression before, during, and after exposure. Five concentrations of each aldehyde were used to construct a concentration response curve, and the concentration eliciting a 50 percent decrease in respiratory rate (RD50) value was determined. Time response curves were similar in both strains of mice exposed to benzaldehyde, cyclohexanecarboxaldehyde, or saturated aliphatic aldehydes. Swiss-Webster-mice exposed to acrolein, crotonaldehyde, or 2-furaldehyde exhibited a continuously decreasing respiratory rate during exposure, particularly at higher concentrations; B6C3F1-mice showed a rapid decrease in respiratory rate at the onset of exposure that was sustained throughout the exposure period. Unsaturated aliphatic aldehydes produced RD50 values ranging from 1 to 5 parts per million (ppm), cyclic aldehydes produced RD50 values ranging from 60 to 400ppm, and saturated aliphatic aldehydes produced RD50 values ranging from 750 to 4200ppm. Alpha, beta unsaturated aliphatic aldehydes were about two orders of magnitude more potent than saturated aliphatic aldehydes, and cyclic aldehydes were one order of magnitude more potent than saturated aliphatic aldehydes. No statistically significant differences in response were found between the two strains of mice. The authors conclude that sensory irritation potency of saturated aliphatic aldehydes diminishes with dehydration constants that determine the degree to which the aldehydes cross link with receptor proteins. Molecular conformation contributes to the sensory irritation process.

5/AU,TI,SO,DE,AB/68 (Item 34 from file: 156)

AU- Matijak-Schaper M; Alarie Y

TI- Toxicity Of Carbon Monoxide, Hydrogen Cyanide And Low Oxygen

SO- Journal of Combustion Toxicology, Vol. 9, pages 21-61, 20 references, 19821982

DE- DCN-128243; Toxic gases; Gas mixtures; Cyanides; Animal studies; Rodents; Exposure chambers; Inhalants; Toxic effects; Biological effects; Median lethal dose; Respiratory rate

AB- The toxicity of carbon-monoxide (630080) (CO), hydrogen-cyanide (74908) (HCN), and low oxygen (7782447) atmospheres were investigated in

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Swiss-Webster-mice. Mice were placed in a glass inhalation chamber designed for head only exposure. Respiratory condition was continuously monitored during exposure. All voluntary body movements were identified, and respiratory response was evaluated. Animals were exposed to CO concentrations of up to 10000 parts per million (ppm) or to HCN concentrations between 10 and 1000ppm. Low oxygen exposures ranged from 5.2 to 9.0 percent. Animals were unaffected by a reduction in oxygen from 20.9 to 9.0 percent. Slight decreases in respiratory rate were seen at 9.0 percent. The median lethal concentration (LC50) for oxygen was 6.7 percent, with three of four mice dying at 6.3 percent and all animals dead at 5.2 percent. The LC50 for CO was 3500ppm, with three of four animals dying at 4840ppm and all animals dead at 6800ppm. For HCN, the LC50 was 166ppm; cyanide had the highest acute inhalation toxicity. A 50 percent decrease in average respiratory rate occurred at 63ppm HCN. Cannulated animals had slightly shorter death times, but LC50s were the same as in mice without cannulas for the same condition. Escape activity was not a sensitive indicator of incapacitation. Recovery from CO exposure was slower after longer exposures. Recovery after HCN exposure was fairly rapid. The authors conclude that CO exerts a direct action similar to that of HCN, although the action of CO is less potent than that of HCN.

5/AU,TI,SO,DE,AB/69 (Item 35 from file: 156)

AU- Popenoe D

TI- Effects Of Paraquat Aerosol On Mouse Lung

SO- Archives of Pathology and Laboratory Medicine, Vol. 103, No. 7, pages 331-334, 13 references, 19791979

DE- DCN-147716; Inhalants; Analytical models; Lung irritants; Biological effects; Pulmonary clearance; Pulmonary function; Laboratory animals; Lung burden; Biochemical analysis

AB- The effects of an aerosol of paraquat (4685147) on the lung were studied in the mouse. Male BALB/c-mice were exposed to an aerosol of paraquat solution at 12 milligrams per milliliter generated by an automatic nebulizer for 15 minutes in a nose only exposure system. Exposed and control mice were killed at 6 hours and 1, 3, 7, 14, and 28 days. Lungs were examined by light and electron microscopy. Toxicity and survival were noted in exposed mice. All mice showed evidence of poisoning at 24 hours. Mortality was limited to the period before 7 days; animals subsequently improved until all survivors appeared asymptomatic by 2 weeks. At 6 hours there was only minimal evidence of inflammation in the lung, with some polymorphonuclear leucocyte infiltration and hyperemia. Electron microscopy generally revealed normal findings. By day 1 the bronchiolar epithelium was totally necrotic and had sloughed off into the lumen in many places. Ultrastructural evidence of damage had increased. Congestion, inflammatory cells and early alveolar disruption appeared. By day 3 there was disruption and fragmentation of both type 1 and type 2 cells. By day 7 there were many foci of increased cellularity. Many proliferating cells were type 2 pneumocytes. Macrophages were numerous in areas of lesions and fibroblast proliferation was evident. By day 14 cellular proliferation was more extensive. Collagen fibrils were present in extracellular spaces, suggesting collagen synthesis. By day 28 areas of cellular proliferation were seen with increased collagen synthesis. The author concludes that paraquat administered directly to the lung produces lesions similar to those produced by other routes of administration.

5/AU,TI,SO,DE,AB/70 (Item 1 from file: 72)

AU- Kaplan H.L.Anzueto A.; Switzer W.G.; Hinderer R.K.

TI- Effects of hydrogen chloride on respiratory and pulmonary function of

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the baboon
SO- <JN> J. TOXICOL. ENVIRON. HEALTH
SO- <PY> 1988
SO- <VO> 23/4 (473-493)
DE- hydrochloric acid; lung function; breathing rate; lung volume
DE- baboon; inhalation; ape
AB- The effects of hydrogen chloride (HCl inhalation on respiratory response during exposure and on pulmonary function during the 3 mo following exposure were studied in the baboon. Each of 4 groups of three anesthetized animals was exposed in a head-only mode for 15 min to air or one of three HCl concentrations (500, 5000, or 10,000 ppm). The acute respiratory response consisted of a concentration-related increase in frequency and minute volume, with a marked decrease in blood PaO2 at the two highest concentrations. The exposures did not cause significant alterations in any of the pulmonary function parameters measured at 3 d and 3 mo postexposure. Thus, nonhuman primates were able to survive short exposures to high concentrations of HCl without any significant effects on pulmonary function during the 3 mo after exposure. Furthermore, comparison of the response of primates and rodents suggests that the human is much less sensitive to the effects of HCl than the mouse.

5/AU,TI,SO,DE,AB/71 (Item 2 from file: 72)
AU- Bond J.A.; Ayres P.H.; Medinsky M.A.; et al.
TI- Disposition and metabolism of (sup 1sup 4C)dibenzo(c,g)carbazole aerosols in rats after inhalation
SO- <JN> FUNDAM. APPL. TOXICOL.
SO- <PY> 1986
SO- <VO> 7/1 (76-85)
DE- dibenzo(c,g)carbazole (0490833); toxicokinetics (0381727); metabolism (0030092)
DE- inhalation (0023732); 7h dibenzo(c,g)carbazole c 14 (0550345); lung absorption (0220777); gastrointestinal absorption (0018982)
AB- Dibenzo(c,g)carbazole (DBC) is a nitrogen-containing polycyclic aromatic hydrocarbon that has been detected in tobacco tars, industrial oils, and diesel engine exhaust fumes. DBC is carcinogenic in respiratory tract tissue of hamsters and in lungs, kidneys, and livers of mice. The purpose of this research was to determine the respiratory tract deposition, distribution in tissues, metabolism, and excretion of DBC in rats after inhalation. Rats were exposed nose-only to 1.1 or 13 mug (sup 1sup 4C)DBC/liter air for 60 min. Activity median aerodynamic diameters for the two concentrations of DBC ranged from 0.7 to 0.8 mum. Urine, feces, and selected tissues were collected for various times after exposure. The fractional deposition for the 1.1 and 13 mug/liter exposure concentrations was similar, 13 and 16%, respectively. The dominant route of excretion of sup 1sup 4C following exposure to either concentration of DBC was the feces, accounting for approximately 95% of the total sup 1sup 4C eliminated. Half-time for fecal excretion was 20 + or - 6 hr (x(bar) + or - SE). Gastrointestinal absorption of (sup 1sup 4C)DBC was 43%. Radioactivity was widely distributed to all tissues examined, with the respiratory tract (lung, trachea, larynx, and nasal turbinates), upper gastrointestinal tract (stomach and small intestine), the liver, and the adrenals containing the highest concentrations of (sup 1sup 4C)DBC equivalents within 1 hr after exposure. At both concentrations of DBC tested, clearance of sup 1sup 4C from tissues was rapid, with approximately 60 to 98% of the initial tissue burden being cleared with half-times ranged from 1 to 16 hr. The remaining 2 to 40% in the tissues was cleared with half-times that ranged from 1.5 to 14 days. Several metabolites were detected in the urine and feces, none of which appeared to be either glucuronide or

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sulfate conjugates. Small quantities of (sup 1sup 4C)DBC were detected in the urine, although quantities were less than 1% of the initial respiratory tract burden of (sup 1sup 4C)DBC. The results from this research indicate that DBC was rapidly absorbed from the lungs and translocated to many tissues. Prior to elimination, primarily in the feces, DBC was extensively metabolized. There appeared to be no effect of exposure concentration on the toxicokinetics of inhaled DBC.

5/AU,TI,SO,DE,AB/72 (Item 3 from file: 72)

AU- Henry C.J.; Kouri R.E.

TI- Chronic inhalation studies in mice. II. Effects of long-term exposure to 2R1 cigarette smoke on (C57BL/Cum x C3H/AnfCum)Fsub 1 mice

SO- <JN> J. NATL. CANCER INST.

SO- <PY> 1986

SO- <VO> 77/1 (203-212)

DE- lung alveolus cell carcinoma (0028145); cigarette smoke (0233055); lung cancer (0028208); adenocarcinoma (0000806)

DE- otitis media (0034876); fibrosarcoma (0017714); macrophage (0028652); mouse (0031367)

AB- Standardized exposure conditions with Kentucky reference 2R1 cigarettes were used to expose 2,053 (C57BL/Cum x C3H/AnfCum)Fsub 1 female mice (nose only) to fresh, whole cigarette smoke. In addition, 1,014 mice were sham-exposed, and 449 mice were held as shelf controls. The protocol entailed exposing mice to smoke (or sham-exposure) on a daily basis, 5 days/week, for 110 weeks and observing remaining mice until death. A large number of animals was used so that the smoke generation and animal-holding systems could be tested and evaluated and yet provide significant numbers of animals for exposure to cigarette smoke for a major portion of their lifetime. Deposition of smoke particulates was estimated to be about 125-200 mug total particulate matter/lung/day. The only lung cancers observed were diagnosed as alveolar adenocarcinomas (AAC). A total of 19 of 978 smoke-exposed mice and 7 of 651 sham-exposed mice were observed with AAC. The difference between the smoke- and sham-exposed groups was not statistically significant at P < or = .05, but the data suggested that the tumors occurred with a shorter latency in the smoke-exposed group (P = .10). The data were analyzed by various methods, including analysis of subsets of the population of animals. A significant increase in the incidence of lung cancer was observed in one subset; however, this difference was not found in the population as a whole or as a result of any other analyses. Under these exposure conditions, 2R1 cigarette smoke would seem to have weak carcinogenic activity in mouse lung tissue. Other changes associated with smoke exposure were increased incidence of pigmented alveolar macrophage accumulation, otitis media, and head and neck fibrosarcomas. However, the incidence of nephritis, hematopoietic cancers (e.g., leukemias, lymphosarcomas, and reticulum cell sarcomas), and pulmonary congestion was significantly higher in the sham-exposed animals.

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